REMARKS

In this Action, the Examiner has variously rejected pending claims 1-13 and 21-38 under 35 U.S.C. §112, first and second paragraphs, for assertedly lacking enablement, assertedly lacking written description, and asserted indefiniteness. The Examiner further rejected claims 1, 4, 5 and 8 under 35 U.S.C. § 102(b) as assertedly anticipated by Lee et al. (Proc. Natl. Acad. Sci. USA 93:1988-92, 1996) (hereinafter "Lee"). The Examiner rejected claims 1-11, 24-28, 30, and 32-38 under 35 U.S.C. § 102(a) as asertedly anticipated by US Patent No. 6,121,416 (hereinafter "'416 patent"). The Examiner rejected claims 21-22 under 35 U.S.C. § 102(b) as assertedly anticipated by Hirohashi et al (Mol. Pharmacol. 53:1068-75, 1998) (hereinafter "Hirohashi"). The Examiner rejected claims 1-11, 24-27 and 29 under 35 U.S.C. § 103(a) as assertedly unpatentable in view of US Patent No. 6,121,416 further in view of US Patent No. 4,975,278 (hereinafter "'278 patent") and also assertedly unpatentable over US Patent No. 6,121,416 in view of Curnis et al. (Nat Biotechnol. 18:1185-90) (hereinafter "Curnis"). The Examiner further rejected claims 21-23 under 35 U.S.C. § 103(a) as assertedly unpatentable over Hirohashi in view of US Patent No. 6,121,416.

Applicants respectfully request reconsideration in light of the amendments and arguments set forth herein.

I. The Subject Matter of the Claims

In general, the subject matter of the pending claims relates to peptide inhibitors of VEGFR-3.

II. Support for the Amendment to the Specification

Amendments to the specification were made to correct spelling errors found by the Applicants. A number of withdrawn claims are dependent method-of-use claims for which rejoinder might be possible at the time that product claims are deemed allowable.

III. Support for the Amendment to the Claims

Support for amendment to claims 1 and 21 may be found for example, at page 14, line 31, which indicates that the peptide of the invention may be any of 6-100 amino acids in sequence length, and page 16, lines 1-2, which states that the peptide may comprise up to 3

conservative amino acid substitutions. The amendment to claims 2-12, and 22-38 are made to correct the Examiner's objections raised in paragraphs 5-7, including dependent claim language and claim dependency.

A number of claims withdrawn from consideration (claims 39, 44, 47-60, 62-68, 70,72-74) were nonetheless amended to eliminate improper dependencies. The Applicants request rejoinder of dependent method claims upon a determination that a product claim is deemed allowable with the understanding that such method claims will depend from (or include all of the limitations of) the allowed product claims.

The amendment includes no new matter.

IV. Patentability Arguments

A. The Rejection of Claims 4-11, 12, and 21-22 Under 35 U.S.C. §112, Second Paragraph, Should Be Withdrawn

The Examiner rejected claims 4-11 under 35 U.S.C. § 112, second paragraph, alleging that these dependent claims recite non-conservative substitutions, even though parent claim 1 recites that the substitutions are conservative substitutions. The Examiner failed to identify with specificity *any* amino acid that the Examiner considered to be a "non-conservative substitution. The term "conservative substitution" finds support and definition throughout the application, including in Tables A, B, and C, and on page 15, lines 13-31. The substitutions recited in claims 4-11 all are defined as conservative substitutions at page 15, lines 13-31. Thus, there is no "antecedent basis" problem, and the rejection should be withdrawn.

The Examiner rejected claim 12 alleging that the recitation of "Y_1" or "Y_2" in the peptide sequence. The Examiner rejected claims 21 and 22 alleging that the terms "X_1", "X_2", "X_3" and "X_4" are indefinite, because it is not clear "which particular" amino acids are within the scope of the claim. Each claim at issue explicitly states that positions Y_1 and Y_2, or X_1, X_2, X_3 and X_4 are specifically contemplated to be amino acids. There is no restriction in the claim that these positions must be "particular" amino acids, as the Examiner implies, and the terms should be interpreted as such, embracing, e.g., amino acids taught in the specification. A worker of ordinary skill in the art would have no difficulty determining whether or not a moiety is an amino acid.

Because the rejected claims clearly define the subject matter of the invention, the rejection should be withdrawn.

B. The Rejection of Claims 1-13 and 21-38 Under 35 U.S.C. §112, First Paragraph – Written Description, Should Be Withdrawn

The Examiner rejected claims 1-13 and 21-38 under 35 U.S.C. § 112, first paragraph, alleging inadequate written description. As authority in support of the rejection, the Examiner cited, e.g., *University of California v. Eli Lilly; University of Rochester v. Searle;* and the PTO's own Written Description Examination guidelines. The Applicants respectfully traverse.

The Examiner's principal and recurring objection appears to be with respect to the open-ended nature of the claim transition "comprising." However, the Examiner has failed to cite any authority indicating that a written description rejection can properly be based on use of this transition. In fact, use of this term, with its "open ended" meaning, has been consistently approved by the PTO and its reviewing court. The Manual of Patent Examining Procedure explicitly recognizes the appropriateness of the open term "comprising" and cites numerous Federal Circuit decisions that have accepted and interpreted it. See, e.g., MPEP (8th Ed., Rev. 2) at §2111.03. Searches using the Patent Office's website search engine indicated that the term "comprising" appears in the claims of more than 1.95 million patents issued since 1976 (and through October 14, 2004), and the term "polypeptide comprising" appears in the claims of over 4100 patents during that time.[1]

The *Eli Lilly* case cited by the Examiner was concerned with a claim that "requires human insulin-encoding cDNA" in a patent that failed to provide a human insulin cDNA sequence. The case did NOT disapprove of the use of the term "comprising" (to permit additional elements) when the elements of the invention were adequately defined.

The *Rochester* case cited by the Examiner involves an extreme fact situation where the patentee claimed a method of administering (any) COX-2 inhibitor in a patent that failed to disclose a single example of a COX-2 inhibitor: "No compounds that will perform the

[1] By way of comparison, the term "polypeptide consisting" appeared in the claims of less than 900 patents in a search performed on October 14, 2004.

claimed method are disclosed, nor has any evidence been shown that such a compound was known." This rare situation is not present here.

Nor do the PTO's written description guidelines express concern over the use of the term "comprising" or the fact that it permits a claim to embrace embodiments with *additional* features beyond what is recited in the claim. Instead, the guidelines concern themselves with "support for the various features of the claimed invention", i.e., support for the claim limitations.

The PTO's own written description Training Materials speak approvingly of the use of the term "comprising" to claim biological inventions. The most relevant example from the Training Materials, Example 14 (reproduced as Exhibit 1), pertains to a claim to a hypothetical genus of proteins claimed with the transition "having" and embracing both a specific amino acid sequence and "variants" having a defined sequence similarity (at least 95%), so long as the variants retain a specified catalytic function of the protein. In the hypothetical example, the specification discloses only a single species of protein falling within the claim, but the specification also provides an assay for identifying all of the variants which are capable of the specified activity. In its analysis, the Patent Office explicitly observed that "the protein claimed may be larger than SEQ ID NO: 3" because the transition "'having' is open language, equivalent to 'comprising'." Even though the hypothetical specification in Example 14 contained only a "single disclosed species," the Patent Office concluded (correctly) that the genus claim was adequately described. "One of skill in the art would conclude that applicant was in possession of the necessary common attributes possessed by the members of the genus."[2]

The "necessary common attributes" of the claims in the present application are very similar to Example 14 of the training materials, insofar as the peptides are claimed with respect to a reference sequence that has a VEGFR-3-binding property, and the variants that are embraced within the claim also are required to retain the binding property. As in Example 14, the application teaches a routine screening assay to identify the peptides with the claimed activity (VEGFR-3 binding activity). [See specification page 42, line 1, to page 43, line 4]. As with Example 14, the proper conclusion is that the claimed invention is adequately described.

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[2] The *Rochester* opinion is relevant in this regard in its discussion of an older *Herschler* decision and the importance of focusing on the points of novelty in the written description analysis.

With respect to the "comprising" issue, the present case stands in a more favorable position than Example 14 or innumerable other issued polypeptide patents insofar as the amended claims have a peptide size limitation of about 100 amino acids. Thus, even though the written description law does not require it, the peptides as presently claimed have a finite number of amino- or carboxy-terminal additional amino acids.

Similarly, the present case stands on more favorable grounds than hypothetical Example 14 insofar as it states that the sequence variation in the defined peptide sequence is conservative substitutions. It is well known that conservative substitutions are less likely to alter conformation and activity than non-conservative substations, which were clearly permitted in Example 14. Also, the application describes more than one working example. (See, e.g., Table 1 and pages 26-27.)

All of the limitations of dependent claims also find adequate descriptive support in the application.

The Examiner further contends that claims 4-11 claim non-conservative amino acid substitutions rather than conservative substitutions based on the listing in Table C (page 31). The specification specifically describes the substitutions recited in these claims and identifies them as conservative substitutions (see page 15, lines 13-31, and Tables A, B and C). Thus, the claimed amino acid substitutions are conservative substitutions as described by the specification.

With respect to claims 21 and 22, the Examiner asserts that the specification does not provide written description for an amino acid X_1, X_2, X_3 in SEQ ID NO: 67. The specification sets out at page 17, lines 11-16, that X_1, X_2, X_3 and X_4 comprise amino acids, and all twenty of the common naturally occurring amino acids are described in the application, as is norleucine. Thus, every element of claims 21-22 defined by the generic term "amino acid" is adequately described.

With respect to claim 30, the Examiner asserts that the specification does not provide written description of a "therapeutic protein amino acid sequence." Page 18, line 26 to page 19, line 7, of the specification describes that the peptide sequence can be attached to any second therapeutic agent, including a cytotoxic agent or a therapeutic protein, such as TNF, wherein that protein therapeutic is a chimeric protein comprising a therapeutic protein amino acid sequence attached to a peptide of the invention. A worker of skill would readily understand that a

therapeutic protein is any protein that has advantages as a therapeutic agent in various diseases, including cancers. A worker of ordinary skill would also understand that a therapeutic protein amino acid sequence was the underlying sequence of any therapeutic protein, such as TNF, and others known in the art, such as interleukin 2 (Davis et al., *Cancer Immunol Immunother.* 52:297-308, 2003), and interleukin-6 (Kreitman et al., *Blood* 79:1775-80, 1992)(abstracts included in Exhibit 2), which may be attached to a peptide of the invention using recombinant DNA techniques. Page 38 of the specification teaches methods for making chimeric and fusion proteins comprising the peptide of the invention by recombinant techniques.

With respect to claim 31, the Examiner asserts that the specification does not provide written description for a peptide that comprises tumor necrosis factor (TNF). Page 38, line 23, to page 39, line 2, describes that plasmids comprising the polynucleotide that encodes the TNF protein may be obtained commercially (e.g. from Novagen). A worker of skill would readily be able to obtain TNF-encoding polynucleotide or polypeptide sequence in order to practice the claimed invention.

With respect to claim 32, the Examiner asserts that the specification does not provide written description for the binding specificity of all antibodies or fragments thereof that may be linked to the peptides of the invention. Page 19, lines 8-11, describes that an antibody contemplated for use by the invention may bind to another antigen on the target tumor or target endothelia, and/or may recognize an antigen on cytotoxic T cells or other immune cells. A worker having ordinary skill in the art would know how to identify and isolate antigens on the surface of endothelial cells and identify tumor antigens (see Hakomori, "Tumor-associated carbohydrate antigens defining tumor malignancy: basis for development of anti-cancer vaccines" *Adv Exp Med Biol.* 2001, 491:369-402; Keogh et al., "Identification of new epitopes from four different tumor-associated antigens: recognition of naturally processed epitopes correlates with HLA-A*0201-binding affinity" *J Immunol.* 2001, 167:787-96, abstracts included in Exhibit 2) which can be targeted by antibodies that are often commercially available. The peptide of the invention is readily conjugated to these antibodies using techniques well-known in the art. Thus, there is adequate written description regarding the specificity of the antibodies contemplated by the invention.

With respect to claim 33, the Examiner asserts that the specification does not provide

written description about which "modification" would increase the half-life of the peptide *in vivo*. Page 19, lines 12-18, describes that standard pharmaceutical and formulation chemistry techniques are used to achieve increased peptide shelf-life and half-life, including glycosylation, pegylation, inducing non-hydrolyzable bonds, mixing with pharmaceutically acceptable carriers and adjuvants, and the like. All of these methods may be used to increase the half-life of the peptide *in vivo*, it is not a matter of choosing one method over the other. A worker of ordinary skill may make any of these modifications using methods readily available in the art to increase peptide half-life. Thus, there is adequate written description for the "modification" in claim 33.

The Examiner asserts that the specification fully describes only one peptide set out in SEQ ID NO: 35, that binds VEGFR-3, and does not provide written description of peptides that bind VEGFR-1, VEGFR-2, NP1 or NP2 as set out in claim 37. The specification at page 20, lines 1-11, describes how to select peptides of the invention that bind at least one growth factor selected from the group consisting of VEGFR-1, VEGFR-2, NP1 or NP2, and teaches at page 42, line 1, to page 43, line 4, methods for assessing binding of the peptide to the receptor of interest.

As stated above, the specification provides adequate written description for the claimed peptides. A worker of skill in the art would understand that the inventors were in possession of the invention at the time of filing the application. The specification teaches the peptide starting amino acids and describes what amino acids may be substituted. In addition to description for the claimed peptides, the specification also provides description for addition of cysteine residues to the C- and N-terminal ends of the peptide and formation of disulfide bonds, conjugation of the peptide to a radionuclide, and generation of a chimeric protein comprising the peptide, therefore providing written description for all claims.

C. The Rejection of Claims 1-13 and 21-38 Under 35 U.S.C. §112, First Paragraph - Enablement, Should Be Withdrawn

The Examiner rejected claims 1-13 and 21-28 under 35 U.S.C. §112, first paragraph, as assertedly not enabled by the description of the specification. The Examiner contends that Applicants have not taught how to make all isolated peptides comprising the claimed peptides (X_1-X_8, $GYWX_1X_2X_3W$, etc.), which may comprise amino acids added onto either or both ends, and contends that there is insufficient guidance as to which larger peptides would maintain structure and function. Applicants respectfully traverse.

As stated above, the term "comprising" is standard claim language accepted by the Patent and Trademark Office which permits a claim to embrace embodiments with *additional* features beyond what is recited in the claim. The specification provides a worker of ordinary skill in the art guidance to make and use the invention as claimed, thereby satisfying the § 112 requirement.

For example, the specification, at page 14, line 14, to page 17, line 18, describes the peptides contemplated by the invention, including the specific conservative amino acid substitutions contemplated. Moreover, the specification at page 35, line 8, to page 38, line 6, teaches methods for making peptides using techniques common in the art such as solid phase synthesis, preparation from a phage library, and recombinant expression systems. Applicants have also described use of the claimed peptides in fusion proteins (see page 38), and use of peptides conjugated to cytotoxic agents and therapeutic proteins (see page 18). A worker of ordinary skill in the art could readily take the peptides taught by the specification and add cysteine residues to the ends of the peptides, or link the claimed peptide to a given amino acid sequence, using the techniques described therein.

In addition to teaching how to make the peptides of the invention, the specification teaches methods for determining if the peptide of the invention binds to and modulates VEGFR-3 activity as well as activities that inhibit VEGF-C binding to VEGFR-3. The specification, at page 42, line 1, to page 53, line 2, teaches *in vitro* assays, such as receptor binding assays, phosphorylation assays, and endothelial cell migration assays to measure VEGFR-3 binding, as well as vascular permeability assays and cell proliferation assays useful in measuring the effects of peptide on VEGF-C mediated VEGFR-3 activity. The specification also describes *in vivo* models to demonstrate the effects of the claimed peptide on VEGF-C/VEGFR-3 mediated activity. Moreover, the specification describes how to use the peptides which have VEGFR-3 binding and/or VEGF-C inhibitory activity such as treating VEGF-C related disorders with protein therapy, gene therapy, immunotherapy, and combination therapies (see pages 53-70).

The Examiner further contends that claims 4-11 recite non-conservative amino acid substitutions based on the listing in Table C (page 31). The specification specifically sets out conservative substitutions contemplated by the invention (see page 15, lines 13-31), and describes how to make such peptides. Thus, the claimed amino acid substitutions are

"conservative" substitutions as described by the specification, and are enabled by the teachings of how to make and use. .

With respect to claims 21 and 22, the Examiner asserts that the specification does not provide guidance for an amino acid having the sequence GWY $X_1X_2X_3W$ or GWY $X_1X_2X_3WX_4$. The specification sets out at page 17, lines 11-16, that X_1, X_2, X_3 and X_4 can be any amino acid, and the specification discloses how to make a peptide having any amino acids at these positions. Moreover, the number of embodiments encompassed by the claims is finite and screening for VEGFR-3 binding activity is routine in the art. Thus, there is sufficient guidance to make and use the invention of claims 21 or 22.

With respect to claim 30, the Examiner asserts that the specification does not provide guidance for a peptide of the invention and a "therapeutic protein amino acid sequence." Page 18, line 26, to page 19, line 7, of the specification describes that the peptide sequence can be attached to any second therapeutic agent, including cytotoxic agent or a therapeutic protein, such as TNF, wherein that protein therapeutic is a chimeric protein comprising a therapeutic protein amino acid sequence attached to a peptide of the invention. A worker of skill would readily understand that a therapeutic protein is any protein that has advantages as a therapeutic agent in various diseases, including cancers. A worker of ordinary skill would also understand that a therapeutic protein amino acid sequence was the underlying sequence of any therapeutic protein, such as TNF, and others known in the art, such as interleukin 2 (Davis et al., *Cancer Immunol Immunother.* 52:297-308, 2003), and interleukin-6 (Kreitman et al., *Blood* 79:1775-80, 1992)(abstracts included), which may be attached to a peptide of the invention using recombinant DNA techniques. Page 38 of the specification teaches methods for making chimeric and fusion proteins comprising the peptide of the invention by recombinant techniques.

With respect to claim 31, the Examiner asserts that the specification does not provide guidance for a peptide that comprises tumor necrosis factor (TNF). Page 38, line 23, to page 39, line 2, describes methods for making a peptide of the invention linked to a TNF molecule, including description of the commercially available source of TNF encoding DNA. An Applicant is not required to put into the application that which is known or readily available in the art, for example "the patent need not teach what is well known in the art," (*Hybridtech, Inc. v Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986)). A worker of skill would readily

be able to obtain TNF encoding polynucleotide or polypeptide sequence in order to practice the claimed invention.

With respect to claim 32, the Examiner asserts that the specification does not provide guidance for the binding specificity of all antibodies or fragments thereof. Page 19, lines 8-11, describes that an antibody contemplated for use by the invention may bind to another antigen on the target tumor or target endothelia, and/or may recognize an antigen on cytotoxic T cells or other immune cells. As set out in section (B) above, a worker having ordinary skill in the art would know how to identify a target tumor antigen or an endothelial cell or T cell antigen and readily generate an antibody to said antigen using routine techniques in the art or obtain an antibody through commercial sources. Also, because the tumor antigens and cell surface antigens are well known in the art and are an extensive list of molecules, if Applicants included every possible antigen it would add vast amounts of information to the application that was well known or readily available to a worker having ordinary skill. The PTO's reviewing court has indicated that information such as this preferably is omitted from applications (*Hybridtech, Inc. v Monoclonal Antibodies, Inc., supra*). Thus, Applicant had provided sufficient guidance to enable the invention in claim 32.

With respect to claim 33, the Examiner asserts that the specification does not provide guidance for a "modification" that would increase the half-life of the peptide *in vivo*. Page 19, lines 12-18, describes that standard pharmaceutical and formulation chemistry techniques are used to achieve increased peptide half-life, including glycosylation, pegylation, inducing non-hydrolyzable bonds, mixing with pharmaceutically acceptable carriers and adjuvants, and the like. Because these are common techniques in the art, a worker of ordinary skill could readily modify a peptide of the invention using any of the above methods.

The Examiner relies on the *Wands* test for enablement, and contends that a worker of skill in the art would have to undergo undue experimentation to practice the claimed invention. Applicants respectfully disagree.

The claims of the application are directed to a limited genus of peptides with specified amino acid length and which bind to a specific cell receptor. The specification fully discloses methods to make the claimed peptides and methods to determine their binding

specificity. Thus, the breadth of the claims does not go beyond the disclosure in the application as filed.

MPEP 2164.05(a) states that the nature of the invention is comprised of both the state of the prior art and the level of skill in the art. The state of the prior art, in turn, relies on what the person of ordinary skill would have known at the time of filing relating to the subject matter of the invention. For the present invention, methods of making peptides, such as chemical synthesis or design of a phage display library, were readily available in the art (see cited art in detailed description and PTO-1449 Form). Also, the VEGFR-3 receptor, ligands for VEGFR-3, and methods for measuring VEGFR-3 activity, including receptor phosphorylation assays, receptor binding assays, cell migration assays, and various *in vivo* assays, were well-known in the art at the time of filing (see cited art in detailed description and PTO-1449 Form). The high level of skill in the biotechnology arts combined with the comprehensive state of the art shown above, indicate that the nature of the present invention is such that a person having ordinary skill in the art would readily be able to make and use the invention.

With respect to the guidance by the inventor and the evidence of working examples, the specification provides methods for making peptides of the invention and all variations thereof. The dependent claims introduce elements known to a worker of ordinary skill. The specification provides methods for determining the VEGFR-3 binding activity and methods for using peptides that bind VEGFR-3 and that inhibit VEGF-C activity. Moreover, the Example beginning on page 74, demonstrates isolation of VEGFR-3 peptides using a phage display library and lists in Table 1 (page 27) numerous examples of VEGFR-3 binding peptides identified by this method. Thus, Applicants provide sufficient guidance of how to make and use the invention as well as provide working examples of isolation and identification of VEGFR-3 binding peptides.

Given the high level of skill in the art and the guidance provided by the Applicants to make and use peptides of the invention, a worker of ordinary skill would not be required to undertake undue experimentation to make or use the invention. The peptides of the invention require a specific sequence or limited variants within that sequence. Additionally, the peptide sequence is of a finite length, such that a limited number of peptides are available and the binding domain of the claimed peptide is short compared to other proteins or peptides.

Therefore, making the peptide of the present invention and screening for activity are performed relatively quickly using routine techniques, and the total number of combinations is orders of magnitude smaller than where a large protein of complex structure is contemplated. The making and screening required by the present invention (peptide synthesis) involves more routine experimentation than that set forth in the facts of *In re Wands,* requiring generation and screening of hybridomas, which the Court of Appeals for the Federal Circuit said was not undue experimentation. Experimentation is not necessarily undue if it is routine in the art (*In re Wands*, 858 F.2d 731 (Fed. Cir. 1988)). Thus, the experimentation required to isolate and identify a VEGFR-3 binding peptide of the invention is routine to a worker having ordinary skill in the art.

As such, Applicants have provided guidance to a worker of ordinary skill in the art to make and use the claimed peptides, and the rejection under 35 U.S.C. § 112, first paragraph, enablement, should be withdrawn.

D. The Rejections of Claims 1-11, 24-28, 30 and 32-38 under 35 U.S.C. §102(a) Should Be Withdrawn

The Examiner rejected claims 1-11, 24-28, 30 and 32-38 under 35 U.S.C. § 102(a) as assertedly anticipated by the disclosure of the '416 patent. The '416 patent allegedly discloses a peptide useful as an insulin growth factor agonist, which comprises a peptide sequence WPVAEWYL. These amino acids allegedly fall within the genus of peptides defined by conservative substitutions in claim 1 as originally filed. The Examiner asserts that this peptide would inherently bind to VEGFR-3 and therefore be encompassed by the present claim.

The amendment to claim 1 obviates the Examiner's rejection. Claim 1 as amended is directed to a peptide wherein the peptide comprises no more than 3 conservative amino acid substitutions relative to the reference sequence GYWLTIWG. Support for the amendment may be found at page 16, lines 1-2, which describes embodiments in which one, two or three conserved amino acid substitutions are introduced at any one time at the eight enumerated positions.

For a reference to anticipate, it must teach each and every element of the claim (MPEP 2131). The peptide disclosed in the '416 patent comprises a peptide having 8

conservative amino acid substitutions relative to the reference sequence GYWLTIWG in claim 1, and therefore does not anticipate the present claims.

As such, the rejection under 35 U.S.C. § 102(a) should be withdrawn.

E. The Rejections of Claims 1, 4-5, 8 and 21-22 Under U.S.C. §102(b) Should Be Withdrawn

The Examiner rejected claims 1, 4-5 and 8 under 35 U.S.C. § 102(b) as assertedly anticipated by the disclosure of Lee. Lee discloses a protein (VRP) comprising the sequence GPHKELDR. The Examiner asserts that most of the amino acids of the peptide in Lee match or are conservative substitutions of the claimed sequence and therefore anticipate the claimed peptide. However, residue X_4 of Lee is lysine (K) while X_4 of the claimed peptide is leucine (L) or a conservative substitution thereof. None of the tables in the specification which identify conservative amino acid substitutions (Tables A-C, pages 29-31) indicate that lysine is a conservative substitution for leucine. Persons in the art do not consider this to be a conservative substitution and the Examiner has not alleged it to be. As such, the peptide of Lee does not satisfy the claim limitation that define position X_4 and cannot anticipate the presently claimed peptides.

The Examiner rejected claims 21-22 under 35 U.S.C. § 102(b) as assertedly anticipated by Hirohashi. Hirohashi discloses a 1502 amino acid rat protein (MLP-1) which comprises a (partial) amino acid sequence (GYWLSLWA). Based on this partial sequence, the Examiner asserts that Hirohashi's protein anticipates claim 21 ($GYWX_1X_2X_3W$), or claim 22 ($GYWX_1X_2X_3WX_4$). The Applicants traverse.

Hirohashi's 1502 amino acid protein has never been shown or suggested to bind VEGFR-3 as required by the claims, and there is no basis to assume that it would. Moreover, the specification states that a peptide as used herein does not include previously described naturally occurring proteins that fortuitously share amino acid sequence identity with the claimed peptide (see page 14, lines 26-31). Finally, the claims, as amended, specify a peptide no larger than about 100 amino acids, and Hirohashi's polypeptide is much larger. Hirohashi does not teach smaller peptides that satisfy the limitation of the claim.

Thus, based on the above, the rejection of clams 1, 4-5, 8 and 21-22 under 35 U.S.C. § 102(b), should be withdrawn.

F. The Rejections of Claims 1-11, 24-27 and 29-31 Under 35 U.S.C. §103(a) Should Be Withdrawn

The Examiner rejects claims 1-11, 24-27 and 29 under 35 U.S.C. 103(a) as assertedly obvious in view of the '416 patent and further in view of U.S. Patent No. 4,975,278.

As stated above, the '416 patent neither discloses nor suggests a peptide as recited in amended claim 1. The secondary reference (the '278 patent) does not cure this deficiency. The '278 patent discloses an anti-neoplastic drug attached to an antibody by an enzyme. A worker of ordinary skill in the art would not be motivated to take the peptide disclosed in the '416 patent, which does not fit within the scope of the invention, and combine it with the teaching of the '278 patent. A worker of ordinary skill in the art would not have a reasonable expectation of success at obtaining the claimed invention based on the disclosure of the '416 and the '278 patents.

The Examiner rejects claims 1-11, 24-26 and 30-31 under 35 U.S.C. 103(a) as assertedly obvious in view of the '416 patent and further in view of Curnis. As stated above, the '416 patent neither discloses nor suggests a peptide as recited in amended claim 1. The secondary reference (Curnis) does not cure this deficiency. Curnis discloses that the TNF alpha molecule may be attached to the peptide sequence NRG to increase the toxicity to certain tumor cells expressing the CD13 molecule. A worker of ordinary skill would have no motivation to combine the teachings of the '416 patent, which disclose a peptide that binds to IGF, with the disclosure in Curnis to create the claimed invention. For all of these reasons, the rejection under 35 U.S.C. 103(a) should be withdrawn

The Examiner rejects claims 21-23 under 35 U.S.C. 103(a) as unpatentable over Hirohashi further in view of U.S. Patent No. 6,121,416. As stated above, Hirohashi, which discloses a large protein of 1502 amino acids that is wholly unrelated to the VEGF family of proteins, neither discloses nor suggests the use of a peptide as claimed herein to bind to VEGFR-3. The '416 patent teaches that peptides can be stabilized by adding cysteine residues to the peptide ends, but does not provide any suggestion or motivation to take the large protein disclosed in Hirohashi and add cysteine residues to obtain the claimed peptide of claims 21-23

which bind to VEGFR-3. Even if the references were combined, a person of ordinary skill would not have arrived at a peptide meeting the sequence, size and activity limitations of the claims. Finally, a worker of ordinary skill would have no reasonable expectation of success in achieving the claimed peptide based on the disclosures of Hirohashi and the '416 patent.

For the above reasons, the rejection of claims 1-11, 24-27 and 29-31 under 35 U.S.C. 103(a) should be withdrawn.

V. Conclusion

For the reasons given above, Applicants submit that claims 1-13 and 21-38 are in condition for allowance and request expedited notice of the same.

Respectfully submitted,

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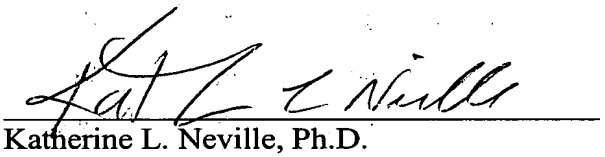
By: 

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Dated: October 20, 2004

Example 14: <u>Product by Function</u>

Specification: The specification exemplifies a protein isolated from liver that catalyzes the reaction of A $\longrightarrow$ B. The isolated protein was sequenced and was determined to have the sequence as set forth in SEQ ID NO: 3. The specification also contemplates but does not exemplify variants of the protein wherein the variant can have any or all of the following: substitutions, deletions, insertions and additions. The specification indicates that procedures for making proteins with substitutions, deletions, insertions and additions is routine in the art and provides an assay for detecting the catalytic activity of the protein.

Claim:

A protein having SEQ ID NO: 3 and variants thereof that are at least 95% identical to SEQ ID NO: 3 and catalyze the reaction of A $\longrightarrow$ B.

Analysis:

A review of the full content of the specification indicates that a protein having SEQ ID NO: 3 or variants having 95% identity to SEQ ID NO: 3 and having catalytic activity are essential to the operation of the claimed invention. The procedures for making variants of SEQ ID NO: 3 are conventional in the art and an assay is described which will identify other proteins having the claimed catalytic activity. Moreover, procedures for making variants of SEQ ID NO: 3 which have 95% identity to SEQ ID NO: 3 and retain its activity are conventional in the art.

A review of the claim indicates that variants of SEQ ID NO: 3 include but are not limited to those variants of SEQ ID NO: 3 with substitutions, deletions, insertions and additions; but all variants must possess the specified catalytic activity and must have at least 95% identity to the SEQ ID NO: 3. Additionally, the claim is drawn to a protein which **comprises** SEQ ID NO: 3 or a variant thereof that has 95% identity to SEQ ID NO: 3. In other words, the protein claimed may be larger than SEQ ID NO: 3 or its variant with 95% identity to SEQ ID NO: 3. It should be noted that "having" is open language, equivalent to "comprising".

The claim has two different generic embodiments, the first being a protein which comprises SEQ ID NO: 3 and the second being variants of SEQ ID NO: 3. There is a single species disclosed, that species being SEQ ID NO: 3.

A search of the prior art indicates that SEQ ID NO: 3 is novel and unobvious.

There is actual reduction to practice of the single disclosed species. The specification indicates that the genus of proteins that must be variants of SEQ ID NO: 3 does not have substantial variation since all of the variants must possess the specified catalytic activity and must have at least 95% identity to the reference sequence, SEQ ID NO: 3. The single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO: 3 which are capable of the specified catalytic activity. One of skill in the art would conclude that

applicant was in possession of the necessary common attributes possessed by the members of the genus.

Conclusion: The disclosure meets the requirements of 35 USC §112 first paragraph as providing adequate written description for the claimed invention.

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Tumor-associated carbohydrate antigens defining tumor malignancy: basis for development of anti-cancer vaccines.

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Tumors expressing a high level of certain types of tumor-associated carbohydrate antigens (TACAs) exhibit greater metastasis and progression than those expressing low level of TACAs, as reflected in decreased patient survival rate. Well-documented examples of such TACAs are: (i) H/Le(y)/Le(a) in primary non-small cell lung carcinoma; (ii) sialyl-Le(x) (SLe(x)) and sialyl-Le(a) (SLe(a)) in various types of cancer; (iii) Tn and sialyl-Tn in colorectal, lung, breast, and many other cancers; (iv) GM2, GD2, and GD3 gangliosides in neuroectodermal tumors (melanoma and neuroblastoma); (v) globo-H in breast, ovarian, and prostate cancer; (vi) disialylgalactosylgloboside in renal cell carcinoma. Some glycosylations and TACAs suppress invasiveness and metastatic potential. Well-documented examples are: (i) blood group A antigen in primary lung carcinoma; (ii) bisecting beta1 --> 4GlcNAc of N-linked structure in melanoma and other cancers; (iii) galactosylgloboside (GalGb4) in seminoma. The biochemical mechanisms by which the above glycosylation changes promote or suppress tumor metastasis and invasion are mostly unknown. A few exceptional cases in which we have some knowledge are: (i) SLe(x) and SLe(a) function as E-selectin epitopes promoting tumor cell interaction with endothelial cells; (ii) some tumor cells interact through binding of TACA to specific proteins other than selectin, or to specific carbohydrate expressed on endothelial cells or other target cells (carbohydrate-carbohydrate interaction); (iii) functional modification of adhesive receptor (integrin, cadherin, CD44) by glycosylation. So far, a few successful cases of anti-cancer vaccine in clinical trials have been reported, employing TACAs whose expression enhances malignancy. Examples are STn for suppression of breast cancer, GM2 and GD3 for melanoma, and globo-H for prostate cancer. Vaccine development canbe extended using other TACAs, with the following criteria for success: (i) the antigen is expressed highly on tumor cells; (ii) high antibody production depending on two factors: (a) clustering of antigen used in vaccine; (b) choice of appropriate carrier protein or lipid; (iii) high T cell response depending on choice of appropriate carrier protein or lipid; (iv) expression of the same antigen in normal epithelial tissues (e.g., renal, intestinal, colorectal) may not pose a major obstacle, i.e., these tissues are not damaged during immune response. Idiotypic anti-carbohydrate antibodies

that mimic the surface profile of carbohydrate antigens, when administered to patients, elicit anti-carbohydrate antibody response, thus providing an effect similar to that of TACAs for suppression of tumor progression. An extension of this idea is the use of peptide mimetics of TACAs, based on phage display random peptide library. Although examples are so far highly limited, use of such "mimotopes" as immunogens may overcome the weak immunogenicity of TACAs in general.

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1: J Immunol. 2001 Jul 15;167(2):787-96.

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Identification of new epitopes from four different tumor-associated antigens: recognition of naturally processed epitopes correlates with HLA-A*0201-binding affinity.

Keogh E, Fikes J, Southwood S, Celis E, Chesnut R, Sette A.

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Forty-two wild-type and analogue peptides derived from p53, carcinoembryonic Ag, Her2/neu, and MAGE2/3 were screened for their capacity to induce CTLs, in vitro, capable of recognizing tumor target lines. All the peptides bound HLA-A*0201 and two or more additional A2 supertype alleles with an IC(50) of 500 nM or less. A total of 20 of 22 wild-type and 9 of 12 single amino acid substitution analogues were found to be immunogenic in primary in vitro CTL induction assays, using normal PBMCs and GM-CSF/IL-4-induced dendritic cells. These results suggest that peripheral T cell tolerance does not prevent, in this system, induction of CTL responses against tumor-associated Ag peptides, and confirm that an HLA class I affinity of 500 nM or less is associated with CTL epitope immunogenicity. CTLs generated by 13 of 20 of the wild-type epitopes, 6 of 9 of the single, and 2 of 5 of the double substitution analogues tested recognized epitopes generated by endogenous processing of tumor-associated Ags and expressed by HLA-matched cancer cell lines. Further analysis revealed that recognition of naturally processed Ag was correlated with high HLA-A2.1-binding affinity (IC(50) = 200 nM or less; $p = 0.008$), suggesting that high binding affinity epitopes are frequently generated and can be recognized as a result of natural Ag processing. These results have implications for the development of cancer vaccines, in particular, and for the process of epitope selection in general.

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1: Cancer Immunol Immunother. 2003 May;52(5):297-308. Epub 2003 Jan 31.

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Immunocytokines: amplification of anti-cancer immunity.

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Many cancers elicit an anti-tumor immune response, which is nevertheless unable to protect the patient. One approach to boost anti-tumor immunity is to target immunostimulatory cytokines to the tumor. Such targeting can be achieved by generating chimeric proteins (immunocytokines) in which the cytokine in question is fused to the C-terminus of a tumor-specific antibody. Immunocytokines containing interleukin-2 (IL-2) have been efficacious in mouse tumor models and have entered clinical trials. Numerous enhancements of immunocytokines are possible, including use of additional stimulatory cytokines, alternate modes of tumor targeting, structural modifications to improve pharmacokinetics, and removal of potentially immunogenic sequences from the fusion protein. In addition, immunocytokines are likely to be efficacious in combination with other therapies, including some forms of chemotherapy and cancer vaccines.

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1: Blood. 1992 Apr 1;79(7):1775-80.

Interleukin-6 fused to a mutant form of Pseudomonas exotoxin kills malignant cells from patients with multiple myeloma.

Kreitman RJ, Siegall CB, FitzGerald DJ, Epstein J, Barlogie B, Pastan I.

Division of Cancer Biology, Diagnosis and Centers, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892.

IL-6-PE4E is a recombinant protein consisting of interleukin-6 (IL-6) fused to a mutant form of Pseudomonas exotoxin in which four basic amino acids are changed to glutamate (PE4E). The chimeric toxin has been previously shown to specifically kill malignant hepatic, prostatic, epidermoid, and myeloma cell lines in vitro. To explore the possible clinical utility of IL-6-PE4E, particularly as an agent for ex vivo purging of marrow for autologous bone marrow transplantation (ABMT), we tested malignant cells from patients with multiple myeloma for sensitivity to this chimeric toxin. Ficoll-purified bone marrow cells were incubated with and without IL-6-toxin for 2 to 3 days. Eight of the 15 myeloma patients had cells that were sensitive to IL-6-toxin as measured by a decrease in the level of protein synthesis. Cells from five patients were very sensitive to IL-6-PE4E, with 50% inhibition of protein synthesis (ID50) achieved at or below 6 ng/mL (7 x 10(-11) mol/L). Cells from three additional patients showed moderate sensitivity, with ID50s between 30 and 140 ng/mL. The remaining seven samples showed little or no sensitivity, with ID50s greater than or equal to 400 ng/mL. Normal bone marrow cells or normal BFU-E and CFU-GM were resistant to the IL-6-toxin even at 1,000 ng/mL. Neither IL-6, IL-2-PE4E, nor an enzymatically deficient mutant of IL-6-PE4E was cytotoxic toward the myeloma cells, indicating that the cytotoxic effect of IL-6-PE4E required the adenosine diphosphate-ribosylation function as well as the specific ligand. Our data suggest that IL-6-toxin could be effective in ex vivo marrow purging in selected multiple myeloma patients who are candidates for ABMT, and that this toxin should also be investigated further for in vivo therapy.

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